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# DEVELOPMENT AND CHARACTERIZATION OF CRISABOROLE LOADED INVASOMAL GEL FOR EFFECTIVE TOPICAL ANTI-INFLAMMATORY EFFECT

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**ABSTRACT**

The present study aimed to develop and characterize a Crisaborole-loaded invasomal gel to enhance topical anti-inflammatory efficacy. Invasomes were prepared using phosphatidylcholine, ethanol, and terpenes by the thin-film hydration method and optimized based on vesicle size and entrapment efficiency. The optimized formulation (IN2) exhibited a vesicle size of 185.65 nm and an entrapment efficiency of 82.26 ± 0.36%, indicating uniform and stable vesicle formation. The optimized invasomes were incorporated into a Carbopol gel base to obtain an effective topical delivery system (IG-2). The invasomal gel displayed excellent viscosity (3425 cps), pH (5.8), drug content (99.12%), and good spreadability and extrudability properties, suitable for dermal application. In-vitro drug release studies revealed a sustained release pattern of 96.65% over 12 hours compared to the pure drug, demonstrating improved permeation and prolonged activity. Kinetic analysis showed that the drug release followed first-order kinetics with an $R^2$ value of 0.9702, suggesting a diffusion-controlled mechanism. Stability studies indicated that the formulation remained physically and chemically stable over 6 months under refrigerated and ambient conditions. The developed Crisaborole-loaded invasomal gel proved to be a promising, stable, and effective system for topical anti-inflammatory therapy, offering better penetration, sustained release, and patient compliance compared to conventional formulations.

## Introduction

Inflammation is a complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells, or irritants, and it plays a vital role in the pathogenesis of several dermatological disorders including atopic dermatitis, psoriasis, and contact dermatitis (Medzhitov et al., 2008). Topical therapy is often preferred for managing such conditions as it allows localized drug delivery with minimal systemic exposure (Prausnitz et al., 2008). However, effective transdermal drug delivery remains challenging due to the low

permeability of the stratum corneum, which acts as a major barrier (Barry et al., 2001).

Crisaborole, a boron-based phosphodiesterase-4 (PDE-4) inhibitor, has shown significant efficacy in treating mild to moderate atopic dermatitis by suppressing inflammatory mediators such as TNF-α, IL-4, and IL-13 (Lebwohl et al., 2016; Hanifin et al., 2012). Despite its therapeutic potential, the drug's poor solubility and limited skin penetration restrict its clinical effectiveness when delivered through conventional formulations like creams or ointments (Huang et al., 2022).

Invasomes are novel phospholipid-based vesicular carriers enriched with ethanol and terpenes, designed to enhance dermal and transdermal drug delivery (Dragicevic et al., 2015). Terpenes serve as natural penetration enhancers that increase vesicle deformability and fluidity, facilitating deeper skin penetration compared to other nanocarriers such as liposomes, niosomes, and ethosomes (Jain et al., 2011; El Maghraby et al., 2014). These systems also offer better stability and improved bioavailability, making them ideal for topical applications (Verma et al., 2010).

Hence, the present study aims to develop and characterize a Crisaborole-loaded invasomal gel to enhance its topical penetration, prolong drug release, and improve therapeutic efficacy against inflammatory skin disorders.

## Material and Methods

### Material

Crisaborole was obtained as a gift sample from a reputed pharmaceutical industry. Soya phosphatidylcholine and terpenes (limonene, cineole, and citral) were procured from Himedia Laboratories Pvt. Ltd., Mumbai, India. Ethanol (absolute, 99.9%) and Methanol (HPLC grade) were purchased from Merck India Ltd., Mumbai. Carbopol 934 and Triethanolamine were supplied by Loba Chemie Pvt. Ltd., Mumbai. Propylene glycol, methyl paraben, and distilled water were used as other supporting excipients. All chemicals and solvents used in this study were of analytical or pharmaceutical grade.

### Methods

#### Formulation of Invasome of Crisaborole

Invasomes of Crisaborole were prepared by mechanical dispersion technique (Table 7.1). Soya phosphatidylcholine was added to ethanol and the mixture was vortexed for 5 minutes. Crisaborole and terpenes were added while the mixture was constantly vortexed and sonicated for 5 minutes. Under constant vortexing, a fine stream of distilled water (up to 10% v/v) was added with a

syringe to the mixture. To obtain the final invasomal preparation, the formulation was vortexed for an additional 5 minutes (Dragicevic-Curic *et al.*, 2010).

**Table 1: Composition of different invasomal formulation**

| Formulation | Drug (2% w/v) | Terpene (%v/v) | Ethanol (ml) | Phosphatidylcholine (%w/v) |
|---|---|---|---|---|
| IN1 | 2 | 0.25 | 10 | 0.25 |
| IN2 | 2 | 0.50 | 10 | 0.25 |
| IN3 | 2 | 0.75 | 10 | 0.50 |
| IN4 | 2 | 0.25 | 10 | 0.50 |
| IN5 | 2 | 0.50 | 10 | 0.75 |
| IN6 | 2 | 0.75 | 10 | 0.75 |

**Characterization of Crisaborole-loaded invasomes**

**Entrapment Efficiency**

Ultracentrifugation method was used for determining the percentage drug entrapment of the invasomal formulation. 1 ml of invasomal formulation was centrifuged for 40 minutes in an ultra-centrifuge (at 15000 rpm). The supernatant was further diluted with ethanol. UV-visible spectrophotometry was used for analysing the Crisaborole content at a wavelength of 250 nm (Ayman *et al.*, 2001; Aggarwal and Kaur, 2005). Percentage drug entrapment was calculated using the equation:

$$\%\ Entrapment\ efficiency = \frac{Total\ amount\ of\ drug - Amount\ of\ Free\ Drug}{total\ amount\ of\ drug} \times 100$$

**Vesicle Size**

Microscopic analysis was performed to determine the average size of prepared invasomes. Formulation was diluted with distilled water and one drop was taken on a glass slide and covered with cover slip (Amnuaikit *et al.*, 2018; Manchanda and Sahoo, 2018).

**Preparation of Crisaborole loaded Invasomal Gel**

Invasomal formulation having good entrapment efficiency, small particle size IN2 was incorporated (equivalent to 2%) in Carbopol 934 gel base. 1%, 2% and 3% i.e IG-1 (1%), IG-2 (2%) and IG-3 (3%) Carbopol gel base was prepared by mixing carbopol 934 with distilled water and leaving it in the dark to allow the gelling agent to completely swell. Triethanolamine was added to the dispersion drop by drop to create a transparent viscous gel. Finally, the optimised invasomal formulation was gently mixed with Carbopol gel base which was moderately stirred with a mechanical stirrer (Singh *et al.,* 2020).

**Evaluation of Crisaborole loaded invasomal gel**

**Determination of physiochemical properties**

Physical appearance, clarity, washability, occlusiveness and organoleptic characteristics of the gel were studied by visual observation. A pH metre was used to evaluate the pH of Crisaborole invasomal gel. The measurements were taken in triplicate, and the average value was determined (Kumar *et al.,* 2022).

**Homogeneity and Grittiness**

Grittiness of the invasomal gel was determined by pressing a small amount of gel between the index finger and the thumb. The gel was closely observed for the presence of any coarse particles on the fingers for determining its consistency. The homogeneity of the gel under evaluation was detected by rubbing a small proportion of gel on the skin at the backside of the hand (Chandra *et al.,* 2019).

**Spreadability**

The spreadability of the invasomal gel was studied by measuring the change in diameter when 500 mg of gel was placed between two horizontal plates of 20×20 cm2 with a standardized weight of 125 g placed over it (Bachhav and Patravale, 2009).

**Extrudability Study**

The prepared invasomal gel was filled in collapsible tubes and its extrudability was estimated in terms of weight in grams required to produce a 0.5 cm ribbon of gel in 10 seconds (Sareen *et al.,* 2011).

**Viscosity**

For determining the viscosity of the invasomal gel Brookfield viscometer (DV-E Brookfield Engineering Laboratories, MA, USA) at 37 °C with spindle No.7 was used.

An appropriate amount of gel was placed onto the centre of the viscometer plate directly below the spindle using the spatula and viscosities were measured.

**Content uniformity analysis of gel**

To validate that the Crisaborole in the developed invasomal gel was homogeneous, 0.5 g samples were drawn from three separate sections of the gel. Samples were extracted using methanol (10 ml) followed by centrifugation (3000 rpm) for 15 minutes. The supernatant was filtered, and Crisaborole content was determined using a UV-visible spectrophotometer with a $\lambda_{max}$ at 250 nm.

***In vitro* drug release**

*In vitro* drug release study was conducted using Franz's diffusion cell with receiver cell volume and effective permeation area of 10 ml and 0.196 $cm^2$ respectively. The donor cell containing the invasomal gel was placed over the receptor cell in which phosphate buffer saline (pH 7.4) was filled. A pre-treated dialysis membrane of molecular weight cut off 12-14 kD was placed between the donor and receptor compartments using a clamp. The experiment was conducted for 24 hours at a temperature of 37 ± 1°C with constant magnetic stirring at 600 rpm. Samples were estimated for Crisaborole content using UV spectrophotometer at 250 nm which were withdrawn from the receptor cell at premediated time gaps i.e., 1, 2, 3, 4, 5, 6, 8 and 12 hours with simultaneously addition of fresh release medium in the receiver compartment to balance the sink conditions. To know the release kinetics of invasomal gel, the data was treated according to different release kinetics models (Kumar *et al.*, 2022).

**Physical stability studies of Crisaborole invasomal gel formulation**

The stability studies of Crisaborole invasomal gel weas performed by determining their physical or chemical attributes during storage. The gel was filled in borosilicate glass container which was observed for 4 months by keeping in two different storage conditions i.e., 4±2°C and 25±2°C with 60±5% RH. The following parameters were analysed during the stability study at specific time periods of 0, 1, 3 and 6 months.

**pH Evaluation**

The pH was evaluated as mentioned earlier.

**Physiochemical Evaluation**

Clarity, washability, occlusiveness and organoleptic characteristics of the gel were studied by visual observation.

**Results and Discussion**

The present study aimed to develop and characterize a Crisaborole-loaded invasomal gel to enhance its topical anti-inflammatory efficacy through improved drug penetration and sustained release. The characterization results (Table 2–9) demonstrated that the prepared invasomal formulations exhibited desirable physicochemical properties suitable for topical application.

The vesicle size of the invasomal formulations ranged from 185.65 nm to 260.36 nm, with the optimized formulation (IN2) showing the smallest size (185.65 nm), which facilitates deeper skin penetration and better drug absorption (Table 2). Smaller vesicle size enhances deformability and allows efficient traversal through the stratum corneum, consistent with previous findings by Jain et al. (2011) and Dragicevic et al. (2015).

The entrapment efficiency (Table 3) varied between 70.36% and 82.26%, with formulation IN2 showing the highest value (82.26 ± 0.36%), attributed to the optimal concentration of phospholipids and ethanol, which improve drug encapsulation within the vesicular bilayer. This high encapsulation ensures prolonged drug release and minimizes drug loss, aligning with observations by El Maghraby et al. (2014).

Further characterization of the invasomal gel formulations (Table 5) revealed pH values in the range of 5.5–5.8, suitable for skin application without irritation. The viscosity (3315–3565 cps), spreadability, and extrudability values indicate good consistency and ease of application. Drug content was above 96%, confirming uniform drug distribution within the gel base.

In-vitro release studies (Table 6, Figure 1) showed that the Crisaborole invasomal gel (IG2) provided sustained drug release up to 96.65% at 12 hours, while the pure drug showed rapid release (94.45% at 4 hours). This indicates the invasomal gel's ability to provide controlled release and prolonged therapeutic action, reducing dosing frequency.

The release kinetics data (Tables 7 and 8) revealed that the optimized formulation IG2 followed first-order kinetics ($R^2$ = 0.9702), indicating that the drug release rate is concentration-dependent. The high correlation with Higuchi ($R^2$ = 0.9479) and Korsmeyer–Peppas ($R^2$ = 0.9545) models further suggests a diffusion-controlled

mechanism governed by both the vesicle and gel matrix.

Stability studies (Table 9) conducted for six months at 4°C and 25°C demonstrated no significant change in color, pH, appearance, or homogeneity, confirming the stability of the developed invasomal gel formulation.

The study concludes that the optimized Crisaborole-loaded invasomal gel (IG2) offers improved drug entrapment, enhanced penetration, and sustained release, making it a promising topical delivery system for effective anti-inflammatory therapy.

**Table 2: Characterization of average vesicle size of Invasome**

| Invasomal Formulation | Vesicle Size* (nm) |
|---|---|
| IN1 | 210.65 |
| IN2 | 185.65 |
| IN3 | 220.36 |
| IN4 | 245.32 |
| IN5 | 260.36 |
| IN6 | 250.25 |

*Average of three determination

**Table 3: Characterization of Entrapment Efficiency of Invasome**

| Invasomal Formulation | % Entrapment Efficiency |
|---|---|
| IN1 | 76.65±0.15 |
| IN2 | 82.26±0.36 |
| IN3 | 73.36±0.22 |
| IN4 | 76.65±0.45 |
| IN5 | 70.36±0.65 |
| IN6 | 71.75±0.28 |

**Table 4: Characterization of optimized formulation of invasome IN2**

| Formulation | Particle Size (nm) | Entrapment Efficiency |
|---|---|---|
| IN2 | 185.65 | 82.26±0.36 |

**Table 5: Characterization of Invasomes gel based formulation**

| Invasomal Gel formulation | Viscosity (cps) | pH | Drug Content (%) | Extrudability (g) | Spreadibility (g.cm/sec) |
|---|---|---|---|---|---|
| IG-1 | 3565 | 5.7 | 97.74 | 155 | 12.25 |
| IG-2 | 3425 | 5.8 | 99.12 | 162 | 11.16 |
| IG-3 | 3315 | 5.5 | 96.65 | 173 | 10.32 |

**Table 6: Cumulative drug release from invasomal gel (IG-2) and pure drug of Crisaborole**

| Time (hrs.) | Cumulative drug release (%) | |
|---|---|---|
| | Crisaborole Invasomal Gel | Pure Drug |
| 1 | 10.32 | 33.36 |
| 2 | 16.65 | 55.58 |
| 3 | 22.23 | 83.32 |
| 4 | 44.52 | 94.45 |
| 5 | 56.65 | - |
| 6 | 69.98 | - |
| 7 | 78.85 | - |
| 8 | 86.65 | - |
| 12 | 96.65 | - |

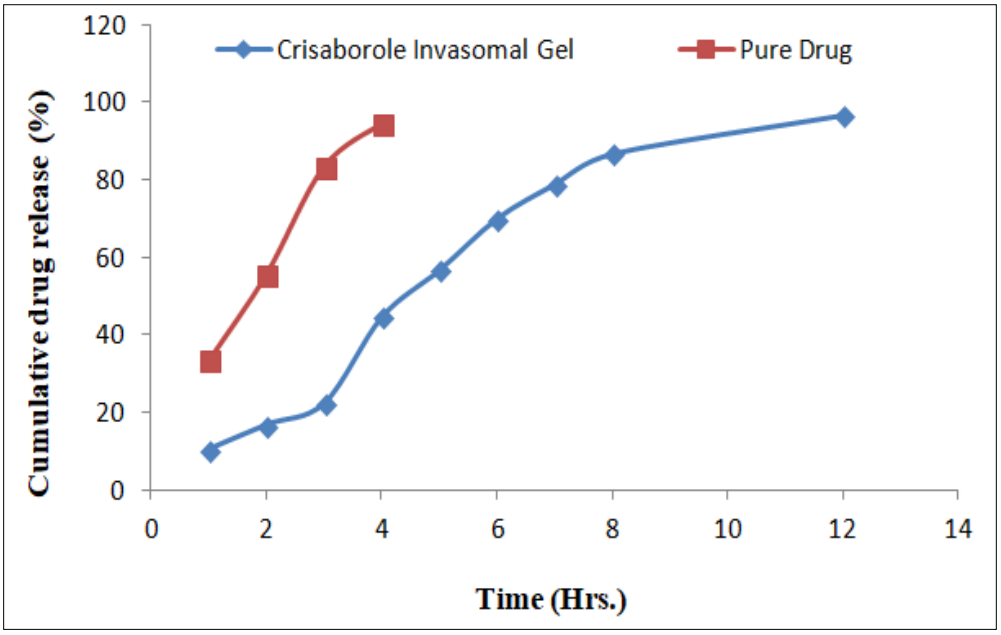


**Figure 1: Cumulative drug release from invasomal gel and plain gel of Crisaborole**

**Table 7: Release Kinetics of Optimized invasomal gel formulation IG-2**

| S. No | Time (Hrs.) | Root Time | Log time | % CDR | % Drug Remain | Log % CDR | Log % CDR Remain |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 0 | 10.32 | 89.68 | 1.014 | 1.953 |
| 2 | 2 | 1.414 | 0.301 | 16.65 | 83.35 | 1.221 | 1.921 |
| 3 | 3 | 1.732 | 0.477 | 22.23 | 77.77 | 1.347 | 1.891 |
| 4 | 4 | 2 | 0.602 | 44.52 | 55.48 | 1.649 | 1.744 |
| 5 | 5 | 2.236 | 0.699 | 56.65 | 43.35 | 1.753 | 1.637 |
| 6 | 6 | 2.449 | 0.778 | 69.98 | 30.02 | 1.845 | 1.477 |
| 7 | 7 | 2.646 | 0.845 | 78.85 | 21.15 | 1.897 | 1.325 |
| 8 | 8 | 2.828 | 0.903 | 86.65 | 13.35 | 1.938 | 1.125 |
| 9 | 12 | 3.464 | 1.079 | 96.65 | 3.35 | 1.985 | 0.525 |

**Table 8: Regression analysis of data for invasomal gel formulation IG2**

| F. Code | Zero order | First order | Higuchi | Pappas |
|---|---|---|---|---|
| IG2 ($R^2$) | 0.9019 | 0.9702 | 0.9479 | 0.9545 |

**Table 9: Stability analysis of Crisaborole invasomal gel formulation IG2**

| Parameters | 1 months | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|
| Temperature (°C) | 4±2°C | 25±2°C | 4±2°C | 25±2°C | 4±2°C | 25±2°C |
| Colour | White | White | White | White | White | White |
| Odour | No | No | No | No | No | No |
| Appearance | Smooth | Smooth | Smooth | Smooth | Smooth | Smooth |
| Clarity | Clear | Clear | Clear | Clear | Clear | Clear |
| pH | 6.82 | 6.80 | 6.82 | 6.72 | 6.770 | 6.25 |
| Homogeneity | Excellent | Excellent | Good | Good | Satisfactory | Satisfactory |
| Washability | Washable | Washable | Washable | Washable | Washable | Washable |

## Conclusion

The present study successfully developed and characterized a Crisaborole-loaded invasomal gel for enhanced topical anti-inflammatory therapy. The optimized invasomal formulation (IN2) exhibited a small vesicle size (185.65 nm) and high entrapment efficiency (82.26 ± 0.36%), confirming its suitability for efficient skin delivery. Incorporation into a Carbopol-based gel (IG-2) resulted in desirable physicochemical properties including ideal viscosity, pH, spreadability, and drug content for topical application. In-vitro release studies demonstrated a sustained drug release (96.65% over 12 hours) compared to the pure drug, indicating improved permeation and prolonged therapeutic effect. Kinetic modeling revealed first-order release with diffusion-controlled behavior, and stability studies confirmed the physical and chemical stability of the formulation over six months. The developed invasomal gel system offers a promising, stable, and cost-effective approach for the topical delivery of Crisaborole, potentially improving drug retention, patient compliance, and

therapeutic outcomes in inflammatory skin disorders.

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